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1806 13

08/09/94

☒ This application has been examined ☒ Responsive to communication filed on 5/5/94 ☒ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), _____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1-9 are pending in the application.
   Of the above, claims 7 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-6 & 8-9 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

III. DETAILED ACTION

1. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately describe and failing to adequately teach how to make and/or use the instant invention.

The specification recites the following on page 3 at line 14.

> "soluble TNFR molecules include, for example, analogs or subunits of native proteins having at least 20 amino acids and which exhibit at least some biological activity in common with TNFRI, TNFRII, or TNF binding proteins....Equivalent soluble TNFRs include polypeptides which vary from these sequences by one or more substitutions, deletions, or additions and which retain the ability to bind TNF or inhibit TNF signal transduction activity via cell surface bound TNF receptor proteins....".

The specification goes on to refer to proteins having "sufficient homology" without really providing the routineer with an exact definition of how such homology is to be determined. Without such guidance, undue experimentation would be required to determine which of the "substantially homologous" proteins fall within applicant's disclosure.

Review of Figures 3 and 4 of the data of Table B does not indicate that the F_c /TNFr fusions are statistically significant when compared with saline. Note that figuring the standard deviation into the data reveals that the figures could be the same. Similar results are shown in Tables C and D. Note that Table D shows the same severity score for the TNFr/F_c as PBS. The day of onset is only accurate to +/- 6 days. That is not accurate to really show that the F_c postpones the onset of arthritis in rats. The data in figures 3 and 4 show similar results. Accordingly, applicants have not really provided data which supports their claims that the F_c/TNFr fusions alone provide treatment for arthritis.

In the response filed 5/5/94, applicants argue that the specification at various positions states that the different mutations, and at page 7 provides specific guidance to the

routineer to adequately make and use the disclosed invention. Applicants conclude that the specification enables testing with a number of well known methods.

Such arguments have been considered but are not deemed persuasive. The specification does contain specific description of a variety of alterations of the TNFr molecules. However, the description is limited at the C-terminus to deletions to amino acid 142. Therefore, applicants have not teachings concerning the molecule past amino acid 142. Accordingly, a broad reading of the specification disclosed as "variants" or "derivatives" is not supported by sufficient intermediate disclosure to define all derivatives. Therefore, in response to applicant's arguments and the specification at page 7, the disclosure is considered sufficient only for C terminal deletions up to amino acids 142. Likewise, the N terminal alterations of amino terminal residues Leu, Pro, and Ala is considered sufficient. However, the random alteration of residues between amino acids 3 and 142 is not supported. Moreover conservative substitutions are also not considered enabled without the practice of undue experimentation. Such a conclusion of non-enablement is reached because applicants have not disclosed a discrete assay to which provides an endpoint for the treatment. In other words, in order to test the "variants" or "derivatives" set forth in the specification, some quantifiable assay must be provided to establish functionality. Applicant's arguments that binding is all that is required is not sufficient because binding alone has not been shown to establish *in vivo* functionality. It is noted that the disclosed invention is a method of treatment, not a product which could have *in vitro* assays. Therefore a different kind of endpoint must be established. Moreover, applicant's *in vivo* data is not conclusively correlated with a reduction in disease. If applicants wish to include different TNFr muteins not actually made, then applicants must provide a specific assay which has been correlated with the method of treatment.

2. Claims 1-6 and 8-9 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

3. Claims 1-6 and 8-9 are rejected under 35 U.S.C. § 101 because the invention as disclosed is inoperative and therefore lacks utility.

This rejection is essentially being made for the reasons argued in the paragraph immediately above. The data presented in the specification is not accurate enough to really show a reduction in joint diameter. Furthermore, the reduction is not shown to

actually improve the condition of the patient. The applicants have no comparison to normal condition to show that the reduction of joint swelling of @0.25mm (fig. 3) is really clinically meaningful. In addition, the data in the Tables A-D does not show that the F_c/TNFr fusion is effective when administered alone. The only apparent effective combination seems to be the combination with the IL1r. Applicants need to provide a showing that the disclosed results are statistically and clinically relevant.

In the 5/5/94 response, applicants argue the following points. Applicants urge that 18.4+ 4.9 is a less effective score than 13.4 + 3.6. Likewise, applicants urge that 18.4 is a 30% increase over 13.4 + 3.6. Applicants urge that the data should be taken at face value and the percent error should not be considered in evaluating the utility of the claimed invention.

These arguments have been considered but are not deemed persuasive. The degree of variation in the results does not establish utility. Within the statistical variation, the results do not show any actual difference because (13.4 + 3.6) is the not less than (18.4 - 4.9). Therefore, the results are not considered sufficiently accurate within the level of error. Accordingly, applicants have not presented statistically meaningful results and the rejection is maintained.

4. Claims 1-6 and 8-9 are rejected under 35 U.S.C. § 101 because the claimed invention lacks patentable utility. The claims are also rejected under §112, first paragraph as failing to teach how to make and/or use the instant invention.

The invention claims the use of recombinant human TNFr to treat arthritis. Such a treatment is inherently an in vivo environment. The dependent claims recite the use of the therapy in humans. To support such claims, applicants have data from rats. The use of rat data to support human claims is not sufficient. The only real use of the claimed method would have to be in humans. However, the generalization from rats to humans is not realistic absent concrete evidence to the contrary. The anatomical differences between the two mammals would render the extrapolation of rodent data to humans unpredictable. Furthermore, rodents are known to often be susceptible to different diseases than humans which would indicate different immune systems. Accordingly, applicants are invited to present persuasive evidence that rats are an art recognized equivalent for humans in the study of arthritis. To support this assertion, the Bloom reference is made of record. Note specifically that line 9 of the second paragraph, right column states that different results were obtained in mice and the "administration of IFN , known to be critical to protection,

was not able to induce a cure.". While this reference deals with cytokines, not so much the antagonists of the claimed invention, the admonition of the first paragraph and the foregoing recitation is considered relevant nonetheless. The targets of the claimed method is the cytokines discussed by Bloom and therefore any method of treatment would have to accommodate the limitations inherent in cytokine therapy as well. Accordingly, the instant invention is considered to lack utility.

Applicants urge in the 5/5/94 response that the specification teaches how to make and/or use the invention, not the claims. Therefore, applicants cannot respond to a rejection which is alleged not to have proper basis. Applicants further respond to that the Bloom reference does not have the proper molecules or the proper disease. As such, applicants urge that the reference cannot be considered persuasive. Furthermore, applicants urge that the Trentham reference shows that rats can be a legitimate model for human utility.

These arguments have been considered but are not deemed persuasive because the reference is used for what it reasonably discloses. That disclosure is the general lack of correlation between the rat immune system and the human immune system. Applicant's citation of the Trentham reference is well taken, however, the reference merely "suggest[s]" that the rat model "may" be appropriate. Such a statement is not unequivocal and therefore, is unpersuasive in view of the reference of record. Furthermore, Trentham's suggestion of using a rat model is further contradicted by US News and World Report article of 8/1/94 which shows that a drug for sepsis has failed. It is noted that sepsis is a disease associated with TNF, the molecule which applicants invention binds. Note that the reference states that the claimed anti-sepsis compound is the fourth potential treatment "to flop". Presumably the companies had successful animal trials prior to embarking on human trials. Therefore, the article indicates that even completely successful animal trials are not always sufficient for human utility. It is noted that applicants have not even submitted data which would establish successful animal trials based on the large degree of error argued above in the objection to the specification. Accordingly, the 8/1/94 article shows that a disease specifically within the scope of applicants stated utility. In addition, the Parrillo reference is submitted for applicant's review. Note specifically, the teaching of the right column, second paragraph of page 1474, which states the nature of organ dysfunction associated with septic shock is "poorly understood". Furthermore, the reference states at page 1476, right col., last two paragraphs, that

"caution" is necessary regarding the use of inhibitors of septic shock. The reference states:

> "The pathogenetic mechanisms of septic shock are complex and interdependent, and many of them represent the body's compensatory response to sepsis and therefore have salutary effects."

Parillo goes on to discuss the disparate results associated with the use of soluble cytokine receptors. Finally, the Oppenheim reference teaches in the right column, second paragraph, pg 234 that the C3H/HeJ strain of mice do not even produce cachectin (TNF) or "other inflammatory mediators". Therefore, this is evidence of the argued distinction of immune systems argued in the instant rejection. If some mammals do not even have inflammatory mediators such as the ligands of the instant inventions, then it is respectfully submitted that insufficient correlation exists between rat and human data to establish utility under §101. In view of the foregoing the rejection is maintained.

5. Claims 1-3 are rejected under 35 U.S.C. § 102(b) as being anticipated by Brennan et al.

The claims recite the use of a TNF antagonist in the mediation of TNF associated arthritis. The claims are not limited to the type of antagonist.

The Brennan reference teaches the inhibition of IL1 production in explanted synovial cell cultures from arthritic human patients. The reduction in the production of IL1 is consistent with the reduction in bone damage and cartilidge destruction associated with rheumatoid arthritis. Note that the reference teaches on pg. 244 first paragraph, "...intra-articular IL1 can induce arthritis.". Therefore, since the source of the synovial cell culture is the human patient, the reference anticipates the rejected claims.

Applicants argue that each and every element of the claimed invention must be taught for the claims to be anticipated. Since the claims recite TNF antagonists, the Brennan reference cannot be used. Such an argument fails to account for the presence of the term "TNF binding protein" in the Markush Group of the claim. Since the antibody of Brennan is a protein and it binds TNF, the antibody is a "TNF binding protein" and the Markush Group is anticipated. Since that term still exists in the claims, the claims are still anticipated and the rejection is maintained.

6. Claims 4-5 and 8-9 are rejected under 35 U.S.C. § 103 as being unpatentable over Brennan in view of Harris and Smith.

The claims recite the following limitations.
A method of treating TNF mediated arthritis with a TNFr.

The Brennan reference has been discussed in paragraph 18 of the §102 rejection. The reference is used as a teaching of expectation of the success because the reference explicitly states that IL1 can induce arthritis and that TNF inhibitors can reduce the production of IL1. The Brennan reference does not teach the use of TNF receptors. However, this is not considered significant because the TNF receptors of the instant claims and anti-TNF antibodies of Brennan operate by the same mechanism. That mechanism is the binding of TNF so that the TNF molecule cannot interact with other receptors, etc.. Therefore, one of ordinary skill in the art would have known that as long as TNF is removed from the environment, the condition of rheumatoid patients would improve.

The Harris reference teaches the use of cytokine inhibitors for the treatment of rheumatoid arthritis on page 1286, end of the 5th paragraph. Therefore, this reference is sufficient to provide the motivation to use the cytokine inhibitors of the instant invention.

The Smith reference provides the sequence of the p80TNFr which was used by applicants in the instant application. The use of such a receptor in the claimed method would have been obvious in view of the cited art set forth above.

The combination of the TNFr of Smith in the methods of therapy set forth in Harris and Brennan references would have been obvious to one of ordinary skill in the art absent evidence to the contrary. The reason for such a conclusion stems from the following disclosures. Because the prior art teaches that an antagonist to TNF will prevent the cause of arthritis (Brennan) and the art recognizes that the claimed compounds were an alternative antagonist to the antibodies of Brennan (see Harris), the routineer would merely substitute the TNFr of Smith for the antibodies of Brennan as taught by Harris to obtain the claimed invention. Therefore, applicant's claimed invention is clearly prima facie obvious absent evidence to the contrary.

The last two claims recite specific dosage amounts and times. However, the dosages are so broad as to represent merely upper and lower extremes. In other words, given the fact that the claimed dose appears to be almost 20 times as strong as that used

in the representative examples, the claimed doses are probably toxic. Therefore, absent some clinical significance they are deemed to be obvious in view of the art.

Applicants respond in the 5/5/94 that the Harris and Smith references are not available as prior art. Applicants are not, however, entitled to priority necessary to enable the invention any earlier than the instant filing date. While applicants did disclose the combination of TNF inhibitors with antibody F_c in previous applications, this disclosure was only in general terms and did not contain any detailed **enabling** disclosure which would teach the routineer how to make and/or use the instant invention. Accordingly, the rejection is maintained for reasons of record and applicants are not entitled to the priority date of anything earlier than the instant filing.

7. Claim 6 is rejected under 35 U.S.C. § 103 as being unpatentable over Brennan in view of Harris ,Capon ,and Hoogenboom further in view of Smith.

The rejected claim recites the use of a fusion F_c region with the TNFr protein.

The Brennan, Harris, and Smith references have been discussed above.

The Capon and Hoogenboom references are added to render the addition of the F_c region to the cytokine receptor (TNFr) obvious. The Capon reference teaches generically, the addition of various receptors and soluble derivatives of these receptors to N-terminus of the F_c region. Moreover, the Capon reference teaches the advantages of using such things in the addition of F_c regions for drugs which interrupt ligand and binding partner interactions. See col 4, lines 16 and following. This is exactly what applicants are claiming. The claimed TNFr is a binding partner that is used to antagonize the interaction TNF (ligand) and the cell bound receptor (binding partner). The patent teaches that the addition of the F_c region increases serum half life (see line 40 of col. 4). The Capon reference does not explicitly mention cytokines. That is why the Hoogenboom reference has been used. The Hoogenboom reference teaches the fusion of the TNFr ligand (TNF) to an immunoglobulin F_c region. Therefore, all one of ordinary skill would have to do is substitute the binding partner for the ligand as explicitly recommended by Capon. Accordingly, because Capon teaches the fusion of F_c with ligand antagonists (binding partners) and the Hoogenboom reference teaches the use of such fusions with the TNF/TNFr ligand/antagonist (binding partner) pair, it would have been

obvious to one of ordinary skill in the art to perform the fusions of Capon and Hoogenboom on the molecules of Smith with the methods of Brennan and Harris.

Applicants argue in the response filed 5/5/94 that the Capon reference fails to disclose the specific fusion of a TNF receptor to the F_c immunoglobulin domain. Further, Capon is argued not to disclose the use of the TNF fusions in inflammation. In response, the Hoogenboom reference states on page 1027, right col., last paragraph, that TNF is a mediator of inflammation. Therefore, the prior art specifically teaches the use of the TNF binding protein fusion proteins for use in treating inflammation. In so far as the Capon reference is concerned. Applicant's attention is directed to col. 2, lines 10 and following, for example. The reference teaches the use of many different hormones and growth factors. In short, the reference provides teaching of a wide variety of different receptors. Moreover, claim 2 is generic in claiming a variety of different receptors which generically include the instant TNF antagonists. Accordingly, the claim itself is presumed valid for the scope and therefore, absent unexpected results applicants specie is considered to be taught by the generic disclosure of Capon.

8. Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL.** See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

9. The oath is defective in the recitation of the prior application number 07/403,421 as being filed in 1985. The application was filed in 1989. A new oath is required to correct the defect.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner

Nisbet whose telephone number is (703) 308-4204 from 9:00 am to 5:00 pm weekdays with the exception of alternating Fridays. If the examiner cannot be reached, the supervisor may be contacted at phone number (703)308-3535.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

TMN
August 8, 1994

DAVID L. LACEY
SUPERVISORY PATENT EXAMINER
GROUP 180
8/8/94